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(54) ALKYLATION PROCESS

(71) We, CANADIAN PATENTS AND DEVELOPMENT LIMITED, a Company duly incorporated under the laws of the Parliament of Canada, to which the Government Companies Operation Act applies, and having its head office at 275 Slater Street, Ottawa 4, Province of Ontario, Canada, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to ring alkylation of aromatic compounds and in particular relates to a novel reductive alkylation process which involves condensation of a carbonyl compound with said aromatic compound in the presence of both an acid condensation agent and a compatible reducing agent, the latter effecting reduction of the intermediate compound resulting from the condensation, concurrent with its formation.

At the present time there are numerous methods of effecting ring alkylation of aromatic compounds, *inter alia* according generally to the following reaction sequence

$$ArH_n \longrightarrow Ar(CHR^1R^2)_mH_{n-m}$$

wherein Ar is an aryl group bearing n replaceable ring hydrogen atoms, m is an integer from 1 to n, and R^1 and R^2 are hydrogen or aliphatic radicals.

One known method of ring alkylation of an aromatic compound is to subject the aromatic compound to chloro-methylation by reacting the aromatic compound with formaldehyde in the presence of hydrochloric acid and zinc chloride and reducing the resultant chloromethyl intermediate such as by catalytic reduction. The process is believed to proceed according to the following reaction sequence

$$ArH_n \xrightarrow[ZnCl_2]{CH_2O,\ HCl} ArH_{n-m}(CH_2Cl)_m \xrightarrow{\text{reduction}} ArH_{n-m}(CH_3)_m$$

However, this process is subject to many disadvantages and in particular it has seldom been possible to use aldehydes other than formaldehyde thus making the process only useful for methylation. Further the process is a two stage process, of which the first stage of chloromethylation is not applicable to very reactive compounds such as many phenols, tars tending to be formed and thus the intermediate chloromethyl substituted aromatic compound is not isolatable for subsequent reduction in the second stage. Further the presence of a chloromethyl group on the aromatic ring tends to reduce the reactivity of the other ring positions and in the majority of cases it is difficult to substitute the ring by more than one chloromethyl group and at most it

has only been possible to substitute the ring by three such chloromethyl groups. It has not heretofore been possible to use this reaction for substituting the ring by more than three methyl groups and the method has usually been restricted to mono-methylation of the ring only for a single two stage process, the total two stages of the process having to be repeated to obtain further methyl nuclear substitution.

Another known process for ring alkylation of an aromatic compound is the formation from the aromatic compound of an intermediate aldehyde or ketone therefrom such as by the Freidel-Crafts or related reaction in which for example a phenol or a phenolic ether is condensed with an acid chloride or acid anhydride in the presence of aluminum chloride and subsequent reduction of the aldehyde or ketone by the Clemmensen Reduction or other method. The process is believed to proceed by the following reaction sequence

$$ArH_n \xrightarrow{\text{Friedel-Crafts}} ArH_{n-m}(COR^1)_m \longrightarrow ArH_{n-m}(CH_2R^1)_m$$

where Ar, n, m and R^1 as as above. However, again this a two stage process involving the isolation of the intermediate aromatic aldehyde or ketone further it is only possible by this method to substitute the ring by at most two alkyl groups and usually one alkyl group and again with this method it is only possible to substitute the ring with groups having CH_2 next to the ring.

A further known method of ring alkylation of aromatic compounds involves the treatment of the aromatic compound with formaldehyde in the presence of an acid and treatment of the product obtained with zinc dust in the presence of an alkali. This process is believed to proceed according to the following reaction sequence

$$ArH_n \xrightarrow[\text{acid}]{CH_2O} (ArH_{n-1})_2CH_2 \longrightarrow ArH_{n-1}CH_3 + ArH_n$$

where Ar and n are as above. However, this process is also a two stage process and is only applicable to very reactive phenols such as phluoroglucinol and β-naphthol and has been used for methylation only. Further, due to the mechanics of the reaction in which the intermediate compound on reaction with the zinc dust and the alkali splits into a methylated aromatic compound and a reactant non-methylated compound, a mixture of such products is obtained and complete conversion of the aromatic compound to a ring methylated compound is impossible even with recycling.

Yet another known method of ring alkylating an aromatic compound involves the Mannich reaction which comprises condensation of the aromatic compound with the hydrochloride of dimethyl amine and formaldehyde and the intermediate dimethyl-aminomethyl compound is subsequently subjected to catalytic reduction. The process is believed to proceed according to the following reaction sequence

$$ArH_n \xrightarrow[\text{Mannich Reaction}]{CH_2O,\ (CH_3)_2NH \cdot HCl} ArH_{n-m}(CH_2N(CH_3)_2)_m$$

$$\xrightarrow[\text{reduction}]{\text{catalytic}} ArH_{n-m}(CH_3)_m$$

where Ar, n and m are as above. Again this process is a two-stage process involving isolation of the intermediate amino compound and is only applicable to more reactive aromatic compounds (which does not include benzene), is usually applied to methylation only and will at most allow trialkylation of the aromatic ring and usually only mono-alkylation.

A still further known method of ring alkylation of an aromatic compound is by means of the Grignard Reaction applied to the aromatic compound and treatment of the Grignard compound so obtained with dimethyl sulphate. The process is believed to proceed according to the following reaction sequence

$$\left.\begin{array}{l} ArH \longrightarrow ArBr \longrightarrow \\ ArH \xrightarrow{CH_3MgBr} \end{array}\right] \quad ArMgBr \xrightarrow{(CH_3)_2SO_4} ArCH_3$$

Again this process is a two stage process involving an intermediate Grignard compound and this process is not applicable to compounds which do not give Grignard reagents such as phenol and with this method it is only possible to monoalkylate the ring.

It is also known that ring alkylation may be carried out by treatment of the aromatic compound with an alcohol or an alkene in presence of a strong acid at a temperature from about 0 to 100°C. The process is believed to proceed according to the following reaction sequence

$$ArH_n \xrightarrow[\text{strong acid at 0—100°C.}]{\text{alcohol or alkene}} ArH_{n-m}R_n$$

where Ar and n are as above and R is an alpihatic or araliphatic radical. While this process is a single stage process it has limited usefulness as rearrangement of the alkyl group of the alkylating reagent may take place and in particular reaction with secondary butyl alcohol frequently gives tertiary butyl derivatives. Further methylated benzenes may isomerize or disproportionate during the reaction for instance to benzene and polymethylbenzenes. The reaction is also reversible and as such complete alkylation is rarely if ever achieved.

Another known single step process for the production of ring alkyl aromatic compound is treatment of the aromatic compound with an alcohol or alkene and the presence of a solid catalyst at high temperatures. The process is believed to proceed according to the following reaction sequence

$$ArH_n \xrightarrow[\text{solid catalyst, high temperature}]{\text{alcohol or alkene}} ArH_{n-m}R_m$$

where Ar, R, n and m are as above. This method is subject to the similar disadvantage as the previous method and in addition only stable and volatile aromatic compounds may be alkylated.

Again another known single stage process for the alkylation of aromatic compounds involves the Friedel-Crafts reaction using aluminum chloride and an aliphatic chloro-compound. The process is believed to proceed according to the following reaction sequence

$$ArH_n \xrightarrow[AlCl_3]{RCl} ArH_{n-m}R_m$$

where Ar, R, n and m are as above. Again the disadvantages of the previous process occur.

Finally, the ring alkylated aromatic compounds may be prepared in a known single stage by reacting the aromatic compounds at a temperature of about 220°C. with an alcohol and the potassium salt of the alcohol according to the following reaction sequence

$$ArH_n \xrightarrow[220°C.]{ROK,\ ROH} ArH_{n-m}R_m$$

where Ar, R, n and m are as above. This process, however, needs high pressure, is only applicable to very reactive compounds such as pyrroles and β-naphthol, and the latter is only mono-methylated. Further labile groups such as ethoxy carbonyl and acetyl are usually split off such as for instance in the cases of pyrroles due to the high temperature used in the process.

In summary therefore, all the heretofore known processes are subject to substantial disadvantages in their applicability to the alkylation of aromatic compounds and many involve two stage procedures with isolation of the intermediate and those which do not are frequently accompanied by isomerization. The known one stage process which avoids these disadvantages, alkylation with an alcohol and its potassium salt under pressure at about 220°C. is only applicable to very reactive aromatic compounds.

The present invention provides a process for the ring alkylation of aromatic com-

pounds such as benzenes, phenols and pyrroles in which the intermediates are not isolated but are reduced as formed or by a continuation of the conditions under which they are formed. As a result, very reactive intermediates are reduced rather than being converted into tars and any starting material regenerated by reduction of the intermediates, and any partially alkylated products are automatically recycled to ensure complete alkylation.

According to the present invention, therefore, there is provided a method of introducing a substituted or unsubstituted alkyl or cycloalkyl group (herein referred to as "alkyl group") onto at least one ring carbon atom of an alkylatable aromatic compound which comprises reacting the aromatic compound with an aldehyde or ketone, or a compound generating an aldehyde or ketone under the reaction conditions (herein referred to as "carbonyl compound") in the presence of strong inorganic acid condensing agent and a reducing agent, the aromatic compound and the aldehyde or ketone, or compound generating the aldehyde or ketone, being stable (as herein defined) under the reaction conditions and the aromatic compound having at least one ring carbon atom having replaceable hydrogen or bearing a substituent removable under the reaction conditions to yield a replaceable hydrogen atom whereby to form with the aldehyde or ketone, or compound generating the aldehyde or ketone under the reaction conditions an intermediate which is reduced to an alkyl or cycloalkyl derivative of the aromatic compound.

Thus, according to the present invention the reducing agent is present from the start of the reaction and thus, the intermediate condensation products of the carbonyl compound with the aromatic compounds are automatically reduced, rather than going to tars. This has the advantage that is not necessary to isolate the intermediate, i.e., the products of the condensation, prior to their reduction which is frequently unworkable because the intermediates are undoubtedly various, often mixtures, and sometimes unstable. Again as the groupings on the aromatic ring formed by the condensation reaction are reduced to alkyl groups, while conditions permitting further condensations are maintained, this allows for poly-substitution of the ring for alkyl groups active the ring and thus facilitate further condensation. Further, it has been found that alkylation can be carried out with the process of the present invention even when the first stage of the reaction, e.g., chloromethylation, has heretofore failed because the intermediate product is so reactive that it normally goes to tar etc., the simultaneous presence of the acid condensing agent and the reducing agent apparently stabilizing the intermediate until it is reduced. Thus even reactive aromatic compounds do not revert to tars before the groupings are reduced. Finally, as will be readily seen where the intermediate upon being reduced forms a mixture of the final product and the starting material then the starting material is automatically present for further reaction with the carbonyl compound to reform the intermediate and thus there is automatic recycling of the reacted starting material. It is therefore possible by means of the process of the present invention to achieve substantially complete conversion. Thus, as both the condensation and the reduction can proceed throughout, any reduction product which is not the product desired e.g. the regenerated reactant aromatic compound or a partially alkylated aromatic compound is automatically recycled to the process for further condensation with the carbonyl compound and reduction of the condensation product.

The process of the present invention is applicable to and has advantage with *inter alia* the following reaction mechanisms which are illustrated using hydriodic acid as the acidic condensating agent and the reducing agent and in which Ar is an aryl group and R is an alkyl group

(I)

$$ArH + R_2CO \xrightarrow[\text{condensate}]{HI} ArCR_2I \xrightarrow[HI]{\text{reduction}} ArCHR_2$$

In the above monoalkylation reaction (I) the process of the present invention has the advantage of eliminating the isolation of the intermediate and is much more convenient than the conventional two stage process. Further the process of the present invention has the particular advantage that it can operate even with the formation of intermediate product which were in the conventional two stage process unstable to an extent that the conventional two stage process was inoperable.

(II)

$$2ArH + R_2CO \xrightarrow[\text{condensate}]{HI} Ar_2CR_2 \xrightarrow[\text{reduction}]{HI} ArCHR_2 + ArH$$

In the above monoalkylation reaction (II) in addition to the advantages with reaction (I) the process of the present invention also recycles the regenerated aromatic compound ArH for subsequent condensation and thus obtain complete monoalkylation. This cannot be achieved in the conventional two stage process. This feature is particularly advantageous as there is no way of knowing *a priori* whether, on monoalkylation, the intermediate condensate product will be as in reaction (I) or reaction (II).

(III)

$$ArH_n \rightarrow Ar(CHR_2)_n$$

In this complete polyalkylation reaction (III) the partially alkylated products are automatically recycled for further condensation and reduction until complete polyalkylation is achieved. Thus the advantages of the process of the present invention in respect to reaction (II) also accrue to the process of the present invention in respect of reaction (III). Further, the reduced groups $—CHR_2$ such as $—CH_3$ and CH_2Cl facilitate the introduction of further substituents, e.g. CIR_2 during condensation and thus aid in completing the polyalkylation. On the other hand unreduced substituents e.g. CIR_2 retard introduction of further such substituents and thus in the conventional two stage process it is only possible to introduce a limited number of alkyl groups ino the ring per cycle.

In particular, therefore, by appropriate choice of reagent quantities, the process of the present invention the condensation and reduction stages can be made repeat until all the replaceable hydrogen in the aromatic nucleus is replaced by alkyl groups whether or not they have been reformed by the reduction stage.

It is essential for the process of the present invention that both the aromatic compound and the carbonyl compounds are stable under the reaction condition. By "stable" is meant herein condensation takes place before any undesirable changes take place in the reactant compounds, e.g. before the reactant compounds undergo ring opening or general decomposition and as the reaction conditions involve acidic conditions, it is generally desirable that the compounds should be stable under acidic conditions. Further it is necessary that the aromatic compound and carbonyl compound be reactive enough to condense and in particular for the aromatic compound to have one or more ring carbon atoms having replaceable hydrogen atoms so as to be reactive with the carbonyl compound under the reaction conditions to form the intermediate. However, the aromatic compound may have present groups such as certain acyl, halogen, carbethoxy and carboxy groups which are automatically removed under the reaction conditions such as elevated temperature, thus generating the aromatic compounds having replacement hydrogen atoms *in situ* during the reaction. Further the aromatic compound must form with the carbonyl compound a reducible condensation intermediate compound as it is essential to the reaction that there be reduction of the intermediate. Suitable aromatic compounds therefore, include heterocyclic aromatic compounds which are five membered ring compounds containing nitrogen in the ring and in particular derivatives of pyrrole as well as six membered carbocyclic compounds including benzene and derivatives thereof. Thus, in particular, the heterocyclic aromatic compound may be pyrrole substituted by at least one and preferably two methyl groups with or without acetayl groups and/or carbethoxy groups. The The carboxy, carbethoxy or acetyl groups are removable from the pyrrole derivative at elevated temperatures above about 100°C. and if it is desired to substitute the positions normally held by these groups by alkyl groups then the reaction may be conducted at the elevated temperature necessary to remove these groups. Particular pyrrole derivatives which may be mentioned as alkylatable by the method of the present invention include 2,4 - dimethyl - 5 - carbethoxy pyrrole, 2,4 - dimethyl-3,5 - dicarbethoxy pyrrole, 2 - methyl - 3 carbethoxy pyrrole, 2,4 - dimethyl - 3-acetyl pyrrole, 2 - carbethoxy - 3 - methyl - pyrrole, 2 - methyl - 5 - carbethoxy pyrrole, 2,3 - dimethyl - 5 - carbethoxy pyrrole, 2,4 - dimethyl - 3 - bromo - 5-carbethoxy pyrrole, 3 - ethyl - 4 - methyl - 5 - carbethoxy pyrrole, 3 - methyl - 4-carbethoxy pyrrole, 2,5 - dimethyl - 3 - carbethoxy pyrrole, 2 - methyl - 3,5 - dicarbethoxy pyrrole, 3 - methyl - 2,5 - dicarbethoxy pyrrole, 2,3 - dimethyl - 5 - carbethoxy pyrrole, 2,3 - dimethyl pyrrole, 2,5-dimethyl pyrrole, 2 - methyl - 5 - car-

boxy pyrrole - 4 - propionic acid diethyl ester and 2,4 - dimethyl pyrrole. Suitable carbocyclic six membered aromatic compounds which may be mentioned include benzene, or benzene substituted by at least one hydroxy, methyl or chlorine group and in particular there may be mentioned benzene, xylenes, phenols, tetrahydronaphthalene or dichlorobenzenes.

The carbonyl compounds reacted with the aromatic compound are aldehydes and ketones and these may suitably have the formula R^3COR^4 wherein R^3 is hydrogen or an aliphatic grouping and R^4 is hydrogen or an aliphatic or aromatic grouping. In particular R^3 may be hydrogen or an alkyl or carboxyl group and R^4 is hydrogen or an alkyl group or R^3 and R^4 together may form with the carbon atom to which there are attached a cycloalkylidene group. Thus, R^3 is suitably methyl, ethyl, isobutyl, tert-butyl, carboxyl, β-carboxyethyl, β-acetylethyl, β-amino-ethyl or hydrogen, R^4 is hydrogen, methyl, ethyl or 3-acetyl-4-methyl-5-carbethoxypyrryl-2- or R^3 and R^4 together with the carbon atom to which they are attached form a cyclohexylidene group. Particular carbonyl compounds which may be mentioned include formaldehyde, acetaldehyde, propionaldehyde, n-butyraldehyde, isobutyraldehyde, paraldehyde, heptaldehyde, laurylaldehyc, stearalehyde, amino-acetaldehyde, acetone, diethyl-ketone, isobutyl-methyl ketone, 3-pentanone, cyclopentanone, cyclohexanone, pyruvic acid, levulinic acid, glyoxylic acid, benzaldehyde, acetophenone, chloroacetone, 2,5-hexane dione and 2-formyl-3-acetyl-4-methyl-5-carbethoxy-pyrrole. The formaldehyde and acetaldehyde are desirably generated *in situ* during the course of the reaction from para-formaldehyde and paraldehyde initially added to the reaction mixture. Other compounds generating the carbonyl compounds include acetals such as dimethyl acetal and 2-biphenyl-carboxaldehyde diethyl acetal and a trimer of stearaldehyde.

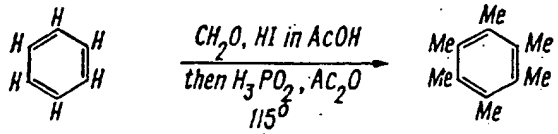
The condensing agent used in the process of the present invention is an acid such as hydriodic acid, hydrobromic acid, sulfuric acid, hydrochloric acid. The condensation is usually carried out in the presence of a solvent which may also be acidic such as acetic acid and particular condensing agent/solvent systems which may be mentioned include hydriodic acid, hydrogen iodide in acetic acid, hydrogen iodide in heptane, hydrogen bromide in acetic acid, hydrogen chloride in acetic acid and sulfuric acid in acetic acid.

In the process of the present invention any reducing system which is compatible with the condensing agent and capable of reducing the intermediate to the final alkylated product may be used and typical reducing agents which may be mentioned include hydrogen iodide solutions, zinc, zinc amalgam or stannous bromide or chloride. In conjunction with the hydrogen iodide there may be present red phosphorous, phosphonium iodide or hypophosphorcus acid which prolong the usefulness of the reducing agent by reconverting the iodine formed during the reduction back to hydrogen iodide. It will be readily seen that hydriodic acid being both a reducing agent and an acid may serve both purposes in the process of the present invention, i.e. the reaction of the carbonyl compound with the aromatic compound may be effected in hydriodic acid alone.

The precise conditions of reaction are not critical and depend primarily upon the reactant carbonyl compound and reactant aromatic compound and as such the reaction may be conducted at elevated or normal temperature and usually under atmospheric pressure. However, in some cases carbethoxy groups can be either retained on the ring by alkylation at lower temperatures or split off and replaced by alkyl groups by alkylating at higher temperatures. The reaction may be conducted in the presence or absence of a solvent as is convenient but is normally conducted in the presence of a solvent such as acetic acid.

The present invention will be further illustrated by way of the following Examples in which the aqueous hydriodic acid used had a density of about 1.94, had been decolourized with phosphonium iodide and when the temperature of the reaction is not indicated there was a rise to 30 or 40°C. consequent on the use of magnetic stirring. Melting points are corrected and the nmr spectra of all the products were consistent with the structures assigned, the Beilstein tests for halogen were negative, and the pyrroles gave positive Ehrlich reactions hot .

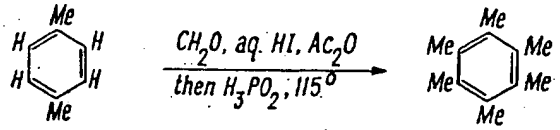
EXAMPLE 1
Preparation of Hexamethylbenzene from Benzene



Hydrogen iodide in acetic acid (20 ml, density 1.6, about 50%), 3 g of paraformaldehyde and 1 ml of benzene were stirred at 20°C for 18 hours in a stoppered flask, then heated for 18 hrs at 90°C. under a reflux condenser. The mixture was cooled, 5 ml of 50% hypophosphorous acid and 20 ml of acetic anhydride were added, and heating continued for 4 hrs at 110°C. It was again cooled, 5 ml of hypophosphoruos acid added, and again heated for 18 hrs at 115°C. The mixture was cooled somewhat, decolorized with hypophosphorous acid, and poured into water. The solid which separated was dried, boiled with 10 ml of pyridine, recovered by pouring the mixture into water, ground and washed with 20 ml of methanol, dried, sublimed (about 100°C. 0.1 mm), and crystallized from 25 ml of methanol as colourless plates (589 mg), m.p. 165—166.5°C. (lit[1] 166.6°) after changing to needles or prisms at ca 105°C. and to plates at ca 145°C. A further 45 mg were obtained from the methanolic mother liquor (total 635 mg, 35%). No aromatic protons were apparent in the nmr spectrum when the intensity was increased 100 times. Anal. Calc. for $C_{12}H_{18}$: C, 88.82; H, 11.18. Found: C, 88.63; H, 11.10.

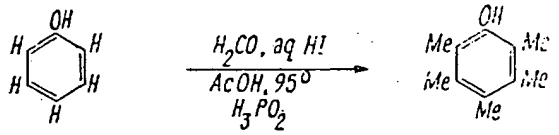
1. H. A. Smith and E. F. H. Pennekamp, J. Am. Chem. Soc., 67, 279 (1945).

EXAMPLE 2
Preparation of Hexamethyl benzene from p-xylene



Hexamethylbenzene was obtained similarly, but more conveniently and in 82% yield, from p-xylene (1 ml), 10 ml of aqueous hydriodic acid, 40 ml of acetic anhydride and 2 g of paraformaldehyde, at 90°C. then at the boiling point of the mixture.

EXAMPLE 3
Preparation of Pentamethylphenol from Phenol

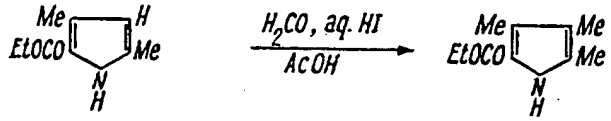


To phenol (4.06 g) in acetic acid (40 ml) was added hydriodic acid (43 ml) and paraformaldehyde (6.47 g). The mixture was kept at 95°C. under nitrogen and stirred for six hours, adding 50% hypophosphorus acid periodically to decolourize it. Ammonium hydroxide was then added dropwise to the cooled (0°C.) an stirred solution until it was basic (ph~8). The product was extracted with ether (3×30 ml), which was dried over anhydrous magnesium sulfate, filtered, and then removed in vacuo to leave the crude product (2.1 g). Several recrystallizations from n-hexane gave the product, 1.64 g (25%), m.p. 127—129°C. (lit.[2] 125°C.). The infrared spectrum had the hydroxyl absorption at 3625 cm^{-1}.

Analysis: Calc. for $C_{11}H_{16}O$: 80.44; H, 9.83; mol. wt. 164. Found: C, 80.12; H, 9.91; mol. wt. 160 (vap. press), 164 (Mass spec.).

2. A. W. Hofmann, Berichte, *18*, 1826 (1885).

EXAMPLE 4
Preparation of 2,3,4-Trimethyl-5-carbethoxy-pyrrole

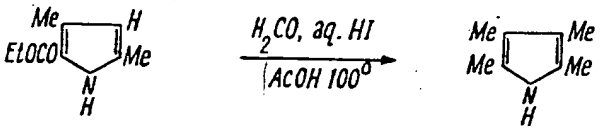


2,4-Dimethyl-5-carbethoxy-pyrrole (0.83 g), acetic acid (10 ml), hydriodic acid (10 ml) and paraformaldehyde (0.60 g) were stirred three hours at 25°C. under nitrogen. Hypophosphorous acid (50%, about 1 ml) was added, dropwise to decolourize the solution. The cooled solution (0.C.) was made basic with ammonium hydroxide and the product was extracted with ether (2×20 ml). The extract was dried over magnesium sulfate, filtered, and the ether removed in a rotating evaporator at 20°C. Recrystallization of the residue from benzene gave the product, 0.58 g (64%), m.p. 125—126°C. (lit[3] m.p. 126°C).

Analysis, Calc. for $C_{10}H_{15}O_2N$: C, 66.27; H, 8.34; N, 7.73 Found: C, 66.35; H, 8.18; N, 7.90.

3. H. Fischer and B. Wallach, Annalen der Chemie, *450*, 125 (1926).

EXAMPLE 5
Preparation of Tetramethylpyrrole

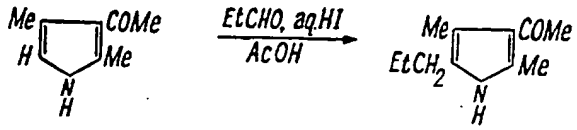


2,4-Dimethyl-5-carbethoxy-pyrrole (1.64 g), acetic acid (25 ml.), aqueous hydriodic acid (25 ml.) and paraformaldehyde (0.589 g), were heated at 95—100°C. for three hours under nitrogen with stirring. The work up was the same as that of 2,3,4-trimethyl-5-carbethoxy-pyrrole in Example 4 except that 2×75 ml of ether was used and care was taken to avoid exposure of the product to air. It was purified by distillation (10 mm, 60°C.) to give 0.628 g (52%), m.p. 106—108°C. (lit[4] m.p. 111—112°C.).

Anal., Calc. for $C_8H_{13}N$: C, 77.99; H, 10.64; N, 11.37.
Found: C, 77.88; H, 10.51; N, 11.22.

4. H. Fischer and E. Bartholomäus, Z. physiol. Chem., *80*, 10 (1912).

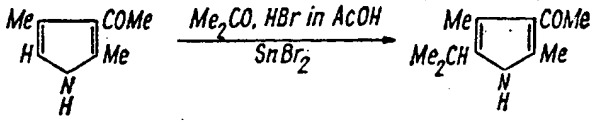
EXAMPLE 6
Preparation of 2,5-Dimethyl-3-acetyl-5-n-propyl-pyrrole



2,4-Dimethyl-3-acetyl-pyrrole (1.02 g), acetic acid (15 ml.), aqueous hydriodic acid (25 ml.) and propionaldehyde (1.74 g), were stirred at 25°C. three hours under nitrogen. The work up was the same as that of 2,3,4-trimethyl-5-carbethoxy-pyrrole in Example 4 except that 2×50 ml ether were used. Recrystallization from benzene gave the product 0.786 g (59%) m.p. 157—158°C.

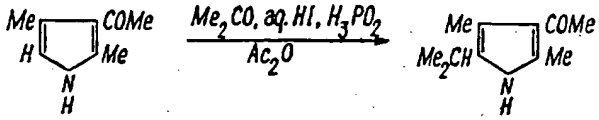
Anal. Calc. for $C_{11}H_{17}ON$: C, 73.70; H, 9.56; N, 7.81;
Found: C, 73.73; H, 9.39; N, 7.79.

EXAMPLE 7
Preparation of 2,4-Dimethyl-3-acetyl-5-isopropyl-pyrrole



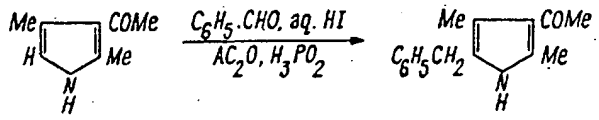
Anhydrous stannous bromide (5 g) was stirred to solution in 20 ml of hydrogen bromide in acetic acid (30—32%). 2,4-Dimethyl-3-acetyl-pyrrole (548 mg) was added and the mixture was warmed to dissolve this, then cooled to 30°C. Acetone (0.6 ml) was added and the solution was stirred at 35°C. for 2-1/2 hrs then poured into water at 10°C. The product was separated and washed with dilute hydrochloric acid then with water. It formed colourless micro-prisms (549 mg, 77%), m.p. 166—167°C. or 173—174.5°C. after changing to cubes at about 136°C. For analysis it was recrystallized from aqueous ethanol as prismatic rods, m.p. 172°C.
Calc. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81.
Found: C, 73.92; H, 9.23; N, 7.88.

EXAMPLE 8
Preparation of 2,4-Dimethyl-3-acetyl-5-isopropyl pyrrole



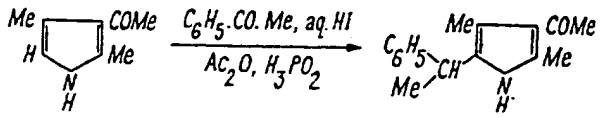
Aqueous hydriodic acid (10 ml) and 2 ml of 50% hypophosphorous acid were cooled and stirred while 10 ml of acetic anhydride was slowly added. 2,4-Dimethyl-3-acetyl-pyrrole (548 mg) was dissolved in the solution, 0.6 ml of acetone added, and the mixture was stirred for 1/2 hr. by which time a yellow precipitate had formed and redissolved and the solution had turned yellow; the final temperature was 37°C. It was poured into 100 ml of water and 30 ml of ammonium hydroxide kept at 20°C. The nearly colourless product separated as plates (662 mg, 92%). At 138°C. these changed to cubes which either melted at 165°C. or turned to irregular needles m.p. 171—173°C. For analysis, it was recrystallized from aqueous ethanol as colourless plates, m.p. 165.5°C or 171.5—173°C.
Anal. Found: C, 73.59; H, 9.48; N, 7.76.

EXAMPLE 9
Preparation of 2,4-Dimethyl-3-acetyl-5-benzyl-pyrrole



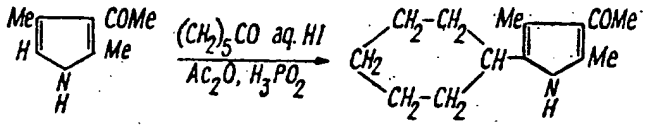
A solution of 10 ml of aqueous hydriodic acid, 10 ml of acetic anhydride and 2 ml of 50% hypophosphorous acid containing 548 mg of 2,4-dimethyl-3-acetyl pyrrole was stirred magnetically while a solution of 0.6 ml of benzaldehyde in 5 ml of acetic anhydride was slowly added over 20 mins. The solution was stirred for 10 mins, then poured into water. The crude product which separated was recrystallized from acetone (thimble) as nearly colourless irregular plates (85%) m.p. 165.5—167°C. after a partial change to prismatic rods above 165°C. Anal. Cal. for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.22; H, 7.50; N, 6.18.

EXAMPLE 10
Preparation of 2,4-Dimethyl-3-acetyl-5-(α-methyl-benzyl)-pyrrole



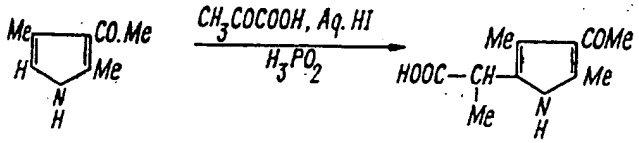
A solution of 0.6 ml of acetophenone in 5 ml of acetic anhydride was slowly added to a stirred mixture of 10 ml of aqueous hydriodic acid, 10 ml of acetic anhydride and 2 ml of hypophosphorous acid containing 548 mg of 2,4-dimethyl-3-acetyl pyrrole. The mixture was allowed to stand for two days at room temperature then poured into water. The crude product which separated was recrystallized from acetone (thimble) as nearly colourless rhombic plates (75%), m.p. 146—148.5°C. Anal. Calc. for $C_{14}H_{15}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.47; H, 7.78; N, 5.79.

EXAMPLE 11
2,4-Dimethyl-3-acetyl-5-cyclohexyl-pyrrole



A solution of 10 ml of aqueous hydriodic acid, 10 ml of acetic anhydride and 2 ml of 50% hypophosphorous acid was stirred magnetically at 40°C. while 548 mg of 2,4-dimethyl-3-acetyl-pyrrole were dissolved in it, 0.5 ml of cyclohexanone was then added, and an additional 0.5 ml of cyclohexanone was added after a few minutes. The solution was stirred at 40°C. for 1-1/2 hrs. then poured into water. The crude product which separated, m.p. 186—188°C. was recrystallized from ethanol as colourless rhombic prisms (82%), m.p. 188.5—189°C. after changing to flat prisms above 153°C.
Anal. Calc. for $C_{14}H_{21}NO$: C, 76.66; H, 9.65; N, 6.39.
Found: C, 76.49; H, 9.50; N, 6.30.

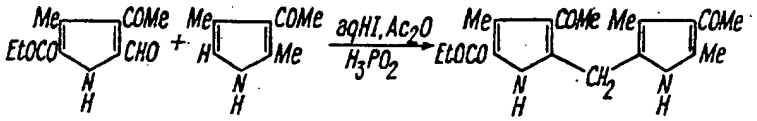
EXAMPLE 12
2,4-Dimethyl-3-acetyl-5-(1-carboxy-ethyl)-pyrrole



A solution of 548 mg. of 2,4-dimethyl-3-acetyl-pyrrole in 10 ml of hydriodic acid and 2 ml of 50% hypophosphorous acid was treated with 0.4 ml of pyruvic acid and stirred for 10 min, when yellow crystals separated. After standing for 2 days at 0°C. the crystals were separated, dried and slurried with 5 ml of water. The resulting colourless product was separated, washed with water, dried and recrystallized from ether (thimble) as pale yellow plates (46%), m.p. 156—158°C. (dec.).
Anal. Calc. for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69; eq. wt. 209.
Found: C, 63.11; H, 6.98; N, 6.80; eq. wt. 207.

EXAMPLE 13

3,4,5'Trimethyl-4,3'-diacetyl-5'-carbethoxy-dipyrryl methane



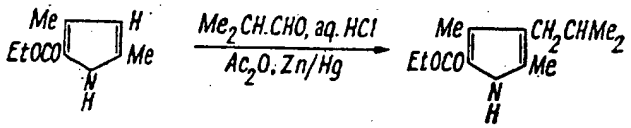
Hydriodic acid (10 ml) was stirred and cooled while 10 ml of acetic anhydride were added slowly. Hypophosphorous acid (2 ml., 50%) and 548 mg of 2,4-dimethyl-3-acetyl-pyrrole were added and the mixture was stirred at room temperature until the latter dissolved. 2-Formyl-3-acetyl-4-methyl-5-carbethoxy-pyrrole (892 mg) was added and the mixture was stirred at 40—45°C. for two hours, then poured into 150 ml of water. The precipitate was separated, dried, slurried and filtered with 15 ml of ethanol, dried, and extracted into 40 ml of acetone (thimble). The product (781 mg) crystallized from the acetone as colourless plates, m.p. 209—212°C. (lit[5] 210°), and concentrating the acetone gave a further 219 mg (total, 73%). The X-ray powder photograph and the nmr spectrum were identical with those of authentic material prepared according to Schlesinger et al[5], for which we found the m.p. to be 210—213°C. the mixed mp. was 209—213°C.

Anal. Calc. for $C_{14}H_{21}O_3N_2$: C, 66.26; H, 7.02; N, 8.13; OEt, 13.08.
Found: C, 66.11; H, 7.23; N, 8.18; OEt, 12.97.

5. W. Schlesinger, A.H. Corwin and L. J. Sargent, J. Am. Chem. Soc., 72, 2871 (1950).

EXAMPLE 14

2,4-Dimethyl-3-iso-butyl-5-carboethoxy-pyrrole



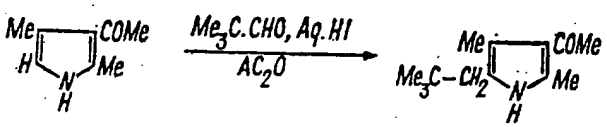
Acetic anhydride (20 ml) was slowly added to 5 ml of concentrated hydrochloric acid with stirring and cooling and 668 mg of 2,4-dimethyl-5-carbethoxy-pyrrole were dissolved in the resulting solution. Amalgamated zinc (10 gm, 20 mesh) and 0.75 ml of iso-butyraldehyde were then added at 20°, and the mixture was stirred for 15 minutes at 20—25°C. The zinc was separated, washed with acetic acid, and the liquids were poured into water to precipitate the crude product. It was dried and extracted into pentane (thimble), the pentane was evaporated, and the residue was recrystallized from aqueous ethanol (13 ml of 55%) as colourless needles (681 mg), m.p. 115—117°C (lit[6], 116—117°C.) after changing to fine needles at about 112°C. and to plates at about 115°C. A further 51 mg were obtained from the mother liquors (total 732 mg, 82%). The nmr spectrum and the X-ray powder photograph were identical with those of authentic material, and the mixed m.p. was 115—117°C.

Anal. Calc. for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27.
Found: C, 70.08; H, 9.67; N, 6.25.

6. J. L. Archibald, D. M. Walker, K. B. Shaw, A. Markovac and S. F. MacDonald, Canad. J. Chem., *44*, 345 (1966).

EXAMPLE 15

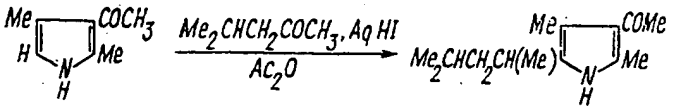
2,4-Dimethyl-3-acetyl-5-neopentyl-pyrrole



2,4-Dimethyl-3-acetyl-pyrrole (548 mg) was warmed to solution in a mixture of 10 ml of aqueous hydriodic acid, 10 ml of acetic anhydride and 2 ml of hypophosphorous acid. The solution was cooled to 35°C. and 0.85 ml of pivalaldehyde were added. The solution was stirred for ten minutes, by which time the initially dark brown color had changed to yellow, then poured into 125 ml of water. The product separated as a colourless powder (769 mg, 93%), m.p. 156—163°C. For analysis, it was recrystallized from ether-pentane, sublimed at 115°C. (10^{-4} mm), and again recrystallized by extraction into hexane (thimble) as long colourless plates, m.p. 166—167°C. after changing to prisms below 130°C. Anal Calc. for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76. Found: C, 75.13; H, 10.30; N, 6.58.

EXAMPLE 16

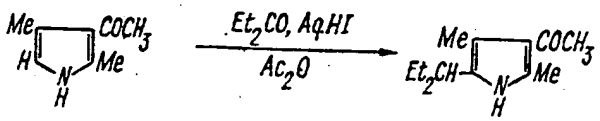
2,4-Dimethyl-3-acetyl-5-(4-methyl-2-pentyl)-pyrrole



Methyl-isobutylketone (1.1 ml) was added to a solution of 548 mg of 2-4-dimethyl-3-acetyl-pyrrole in aq. hydriodic acid (10 ml), acetic anhydride (10 ml) and hypophosphorous acid (2 ml). The solution was stirred for four hours; then poured into a mixture of 150 ml of water and 30 ml of ammonium hydroxide. The product separated as tiny colourless prisms, m.p. 142—143°C. some changing to plates at 120°C. Anal. Calc. for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.81; H, 10.37; N, 6.38.

EXAMPLE 17

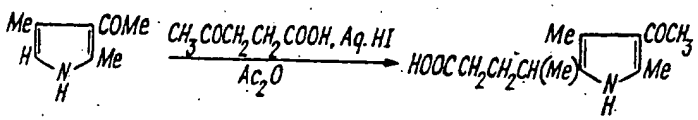
2,4-Dimethyl-3-acetyl-5-(3-pentyl)-pyrrole



3-Pentanone (0.85 ml) was added to a solution of 548 mg of 2,4-dimethyl-3-acetyl-pyrrole, in 10 ml of aq. hydriodic acid, 10 ml of acetic anhydride and 2 ml of hypophosphorous acid. The solution was stirred for 1-3/4 hours then poured into 200 ml of water to precipitate the product as tiny nearly colourless prisms (651 mg, 79%) m.p. about 186—189°C. For analysis it was recrystallized from ethanol as colourless plates, m.p. 188.5°C. after a solid phase change at 135°C. Anal. Calc. for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76. Found: C, 75.13; H, 1004; N, 6.78.

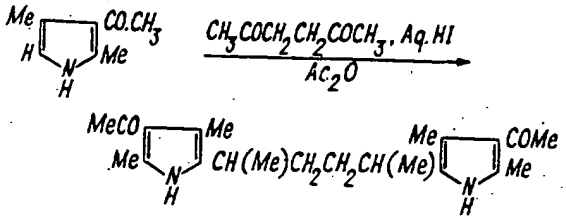
EXAMPLE 18

2,4-Dimethyl-3-acetyl-pyrrole-5-(4-pentanoic) acid



A solution of levulinic acid (0.6 ml) in 5 ml of acetic anhydride was slowly added to a solution of 548 mg of 2,4-dimethyl-3-acetyl-pyrrole in aqueous hydriodic acid (10 ml), acetic anhydride and hypophosphorous acid (2 ml). The solution was stirred for twelve hours then the volatile solvents were removed in a vacuum desiccator over potassium hydroxide. Water (10 ml) was added to the residue to yield the product as an oil which soon solidified to salmon coloured prisms (742 mg), m.p. 177—179°C. For analysis, it was recrystallized from acetone (thimble) as nearly colourless prisms, m.p. 177—178°C. Anal. Calc. for $C_{12}H_{17}NO_3$: C, 65.80; H, 8.07; N, 5.90; eq. wt. 237. Found: C, 66.03; 8.20; 5.91; eq wt. 234.

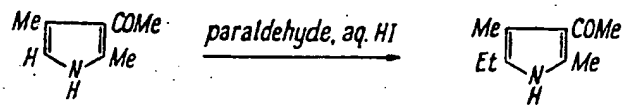
EXAMPLE 19
2,5-Bis-(3,5-dimethyl-4-acetyl-2-pyrryl)-hexane



2,5-Hexandione (1 ml) was added to a solution of 548 mg of 2,4-dimethyl-3-acetyl-pyrrole in 10 ml of aqueous hydriodic acid, 10 ml of acetic anhydride and 2 ml of hypophosphorous acid. The solution was stirred for 1-1/2 hours then poured into 150 ml of water to precipitate the nearly colourless product (442 mg), m.p. 263—268°C. For analysis, it was twice recrystallized from acetone (thimbles) as a colourless crystalline powder, m.p. 275—279°C. after changing to needles at 271°. Anal. Calc. for $C_{22}H_{32}N_2O_2$: C, 74.12; H, 9.05; N, 7.86. Found: C, 74.01; H, 9.04; N, 7.94.

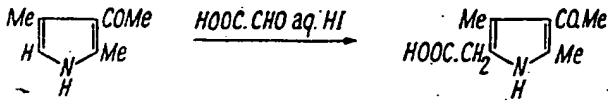
It will be seen from the above Example that besides ring alkylation the use of dicarbonyl compounds such as 2,5-hexane dione makes if possible for the alkyl group to bridge two rings.

EXAMPLE 20
2,4-dimethyl-3-acetyl-5-ethyl-pyrrole



A solution of 2,4-dimethyl-3-acetyl-pyrrole (548 mg) in 10 ml of aqueous hydriodic acid containing a little solid phosphonium iodide was cooled in an ice-salt bath. Paraldehyde (0.35 ml) was added and the solution was stirred for 4-1/2 hrs. without further cooling. The solution was then added to 100 ml of ice water to precipitate the light brown product (385 mg, 58%), m.p. 153—160°C. For analysis, it was sublimed in vacuo then recvrystallized from ether (thimble) as grey needles, m.p. 163°C. after changing to plates at 140°. Anal. Calc. for $C_{10}H_{15}O$: C, 72,69; H, 9.15; N, 8.48. Found: C, 72.67; H, 8.88; N, 8.69.

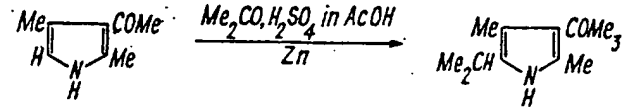
EXAMPLE 21
2,4-Dimethyl-3-acetyl-pyrrole-5-acetic acid



Glyoxalic acid monohydrate (500 mg) was added to a solution of 548 mg of 2,4-dimethyl-3-acetyl-pyrrole in 10 ml of aqueous hydriodic acid and 2 ml of hypophorcus acid. The solution was stirred for one hour at 15°C. The yellow crystalline solid was filtered off, washed with ether, dried, then slurried with 5 ml of water. The solid was again separated, washed with 5 ml of water, dried and extracted into 40 ml of ether (thimble). When the ether solution was concentrated the produce separated as yellow prisms (550 mg), m.p. 195—205°C. For analysis, it was recrystallized by dissolving it in 40 parts of cold 50% aqueous acetone, boiling off the acetone, and cooling. It separated as nearly colourless prismatic rods, m.p. 206—210°C. after changing to prisms at 155° and evolving gas at 175°; presumably it decarboxylated to

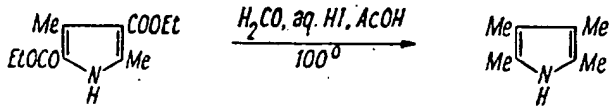
the 5-methyl derivative before melting. Anal. Calc. for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18; eq. wt. 195. Found: C, 61.35; H, 6.90; N, 7.10; eq. wt. 197.

EXAMPLE 22
2,4-Dimethyl-3-acetyl-5-isopropyl-pyrrole



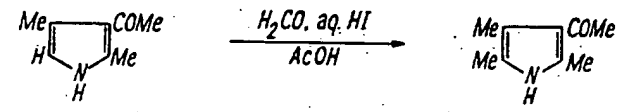
2,4-Dimethyl-3-acetyl-pyrrole (548 mg), 1 ml of acetone and 10 gm of amalgamated zinc (20 mesh) were added to a solution of 1 ml of concentrated sulfuric was sublimed in vacuo then recrystallized from ether (thimble) as grey needles, m.p. liquid was decanted from the zinc into 100 ml of water forming a solution from which the crude product separated at 15°C. (174 mg, m.p. 164—169°C. after the usual solid phase changes). For analysis, it was extracted into ether (thimble) then recrystallized from 3 ml of aqueous ethanol as nearly colourless elongated prisms, m.p. 170—172°C. (171—173° when mixed with the product of Example 8) after a solid phase change at 142°. Anal. Calc. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.60; H, 9.40; N, 7.92.

EXAMPLE 23
2,3,4,5-Tetramethyl-pyrrole



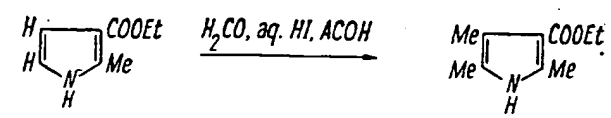
2,4-Dimethyl-3,5-dicarbethoxy-pyrrole (2.4 g), acetic acid (35 ml) aq. hydriodic acid (35 ml) and paraformaldehyde (1.2 g) were heated at 100°C. for four hours under a stream of nitrogen. The crude product was obtained as in Example 5 then distilled (15 mm, 65°C) to yield 0.44 g (36%), m.p. 107—109°.

EXAMPLE 24
2,4,5-Trimethyl-3-acetyl-pyrrole



2,4-Dimethyl-3-acetyl-pyrrole (0.68 g), acetic acid (15 ml), aq. hydriodic acid (15 ml) and paraformaldehyde (0.6 g) were stirred for three hours under nitrogen at room temperature. The crude product was isolated as in Example 4 (2,3,4-trimethyl-5-carbethoxy-pyrrole) then crystallized from benzene to yield 0.55 g (73%) of colourless elongated prisms, m.p. 204—207°C. (lit. 207° H. Fischer and W. Zerweck, Berichte 56, 523 (1923)). Anal. Calc. for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.29; H, 8.68; N, 9.38.

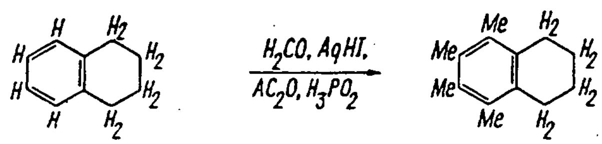
EXAMPLE 25
2,4,5-Trimethyl-3-carbethoxy-pyrrole



2-Methyl-3-carbethoxy-pyrrole (0.99 g), acetic acid (15 ml), aq. hydriodic acid (20 ml) and paraformaldehyde (0.78 g) were stirred for three hours at room temperature. The crude product was isolated as in Example 4 (2,3,4-trimethyl-5-carbethoxy-pyrrole) and sublimed (82°C., 4×10^{-3} mm) as fine colourless needles (75%), m.p. 103—103.5°C. (lit. 104—105° L. Knorr and K. Hess, Berichte 44, 2762 (1911)). Anal. Calc. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.35; H, 8.17; N, 7.88.

EXAMPLE 26

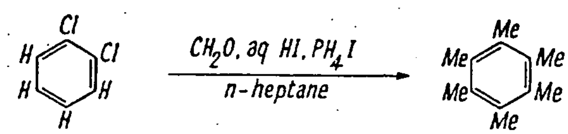
5,6,7,8-Tetramethyl-1,2,3,4-tetrahydronaphthalene



1,2,3,4-Ttetrahydronaphthalene (1 ml) was added to a mixture of paraformaldehyde (2 g), aq. hydriodic acid (10 ml) and acetic anhydride (40 ml). The mixture was then stirred and heated under reflux for 4-1/2 hr. at 90—100°C, then at ca 116° for 5 hr. During the heating, the solution was prediocilally cooled to 60° and decolorized with hypophosphorous acid (total 7 ml). The warm solution was added to 125 ml of water, the resulting mixture was cooled, and the crystalline crude product was separated. This was boiled for 5 min. with pyridine and the hot solution poured into boiling water (125 ml) containing 10 ml of acetic acid. The mixture was cooled and the product was separated, dried, sublimed (75°C., 1×10^{-4} mm), and extracted into 20 ml of methanol. When the solution was concentrated then allowed to cool, 925 mg of the product separated and a further 94 mg were obtained by concentrating the mother liquors. The product formed large colourless plates, m.p. 81.5—82°C. (M. C. Kleetzel, R. P. Dayton and H. L. Herzog report 79—79.5°. J. Am. Chem. Soc. 72, 273 (1950)). Anal. Calc. for $C_{14}H_{20}$: C, 89.29; H, 10.71. Found: C, 89.43; H, 10.49.

EXAMPLE 27

Preparation of hexamethylbenzene from o-dichlorobenzene



A mixture of o-dichlorobenzene (1.47 g) aq. hydriodic acid (20 ml), paraformaldehyde (2.4 g) and n-heptane (20 ml) was stirred by a "Vibro-Mischer" at 95°C (bath temp.) under reflux for 10 hours, decolorizing it periodically with phosphonium iodide. The heptane layer was then separated and washed with 20% aqueous pyridine (2×25 ml), with 10% hydrochloric acid, and with water. It was then dried and the heptane was evaporated. The residue was recrystallized from pentane as colourless crystals (621 mg, 38%). For analysis, it was sublimed (65°C., 1×10^{-2} mm), m.p. 164—165°C. Found: C, 88.64; H, 11.31.

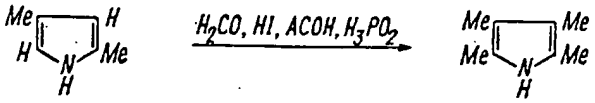
EXAMPLE 28

2,3,4,5-Tetramethyl-pyrrole from 2,4-dimethyl-3-acetyl-pyrrole

2,4-Dimethyl-3-acetyl-pyrrole (1.58 g) in 25 ml of acetic acid was added in five portions during one hour to a stirred mixture of paraformaldehyde (2.07 g), aq. hydriodic acid (25 ml) and hypophosphorous acid (3 ml) maintained at 115°C. under nitrogen. The mixture was heated at 115°C. for a further three hours, and the crude product then isolated as in Example 4 above. Distillation (65°C, 10 mm) gave 996 mg (68%) of colourless crystals, m.p. 108—110°C. Found: C, 77.74; H, 10.59; N, 11.19.

EXAMPLE 29

Tetramethyl-pyrrole from 2,4-dimethyl-pyrrole



2,4-Dimethyl-pyrrole (2.06 g) in acetic acid (50 ml) was added over 2 h. to a stirred solution of paraformaldehyde (5.21 g) in hydriodic acid (75 ml), acetic acid (25 ml) and hypophosphorous acid (6 ml) at 105°C under nitrogen. The solution was heated 4 h. longer then brought to pH 9 with ammonium hydroxide at 0°C. Isolated as in Example 5 and washed with a little pentane, the colourless product (0.996 g, 37%) melted at 107—109°C. The analytical sample, m.p. 109—111°C, had been redistilled (60°, 8 mm). Anal. Found: C, 77.94; H, 10.56; N, 11.21.

EXAMPLE 30

2,4-Dimethyl-3-acetyl-5-isobutyl-pyrrole

(a) 2,4-Dimethyl-3-acetyl-pyrrole (548 mg) was dissolved in hydriodic acid (10 ml), acetic anhydride (10 ml) and hypophosphorous acid (2 ml). Isobutyraldehyde (0.75 ml) was added and the solution was stirred for 35 min. No precipitate formed. Water precipitated a yellow iodine complex (864 mg), m.p. unsharp from 90°, Beilstein test for halogen positive. This was converted into the desired product by dissolving is in ethanol and adding ammonium hydroxide. For analysis it was recrystallized from aqueous ethanol, m.p. 152° after changing to smaller crystals at 125°. Anal. Calc. for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.40; H, 9.73; N, 7.43.

(b) When the above reaction was run in the presence of a little added phosphonium iodide, the colour faded within 1 min. and after 5 min. water precipitated the colourless product (0.7 g, 91%). It melted at 150—152° (phase change at 125°) after being recrystallized from ethanol.

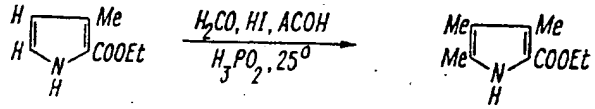
EXAMPLE 31

2-Methyl-4,5-diethyl-3-carbethoxy-pyrrole

A solution of 612 mg of 2-methyl-3-carbethoxy-pyrrole in 10 ml of hydriodic acid, 10 ml of acetic anhydride and 2 ml of hypophosphorous acid was stirred while 0.35 ml of paraldehyde was dropped in. Stirring was continued for 1/2 h. and the solution was then poured into water. For analysis, the pale yellow micro-crystals which separated (0.45 g, 53%, m.p. 104—106°) were recrystallized from aqueous ethanol. Anal Calc. for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.67. Found: C, 68.73; H, 9.09; N, 6.85.

EXAMPLE 32

The preparation of 2,3,4-trimethyl-5-carbethoxy-pyrrole

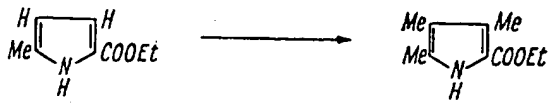


A solution of 2-carbethoxy-3-methyl-pyrrole [1] (0.306 g, 2 millimols) and paraformaldehyde (0.3 g) in acetic acid (5 ml) hydriodic acid (5 ml) and hypophosphorous acid (1 ml) was stirred for 2 1/2 hrs at 25° then poured into water. The mixture was made alkyline with ammonium hydroxide and the product then separated, dried and recrystallized from ether-n-pentane as colourless needles (0.121 g); 33%), m.p. 127—129° (lit [2] m.p. 128°). Anal. Calc. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.09; H, 8.19; N, 7.79.

[1] A. H. Corwin and J. L. Straughn, J. Amer. Chem. Soc., *70*, 1416 (1948)

[2] H. Fischer and H. Orth, "Chemie des Pyrols", Vol. 1, p. 239, Akademische, Leipzig 1934.

EXAMPLE 33
The preparation of 2,3,4-trimethyl-5-carbethoxy-pyrrole

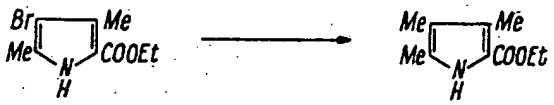


As in Example 32 but using 2-methyl-5-carbethoxy-pyrrole [3]. It formed colourless needles (50%), m.p. 127—129°. Anal. Found: C, 66.42; H, 8.40; N, 7.89.
3) H. Fischer and H. Orth. loc. cit. p. 238.

EXAMPLE 34
The preparation of 2,3,4-trimethyl-5-carbethoxy-pyrrole

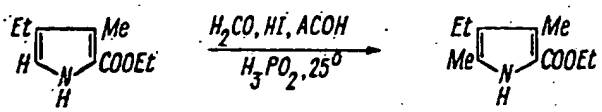
As in Example 32 but using 2,3-dimethyl-5-carbethoxy-pyrrole [4]. It formed colourless needles (72%), m.p. 127—129°. Anal. Found: C, 66.13; H, 8.41; N, 7.71.
4) H. Fischer and H. Orth, loc. cit. p. 238.

EXAMPLE 35
The preparation of 2,3,4-trimethyl-5-carbethoxy-pyrrole



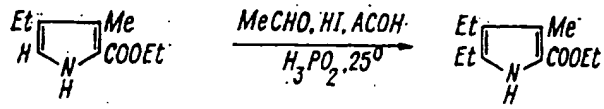
As in Example 32 but using 2,4-dimethyl-3-bromo-5-carbethoxy-pyrrole [5]. It formed colourless needles (60%). m.p. 126—127°. Anal. Found: C, 66.20; H, 8.30; N, 7.88.
5) H. Fischer and H. Orth. loc. cit. p. 92.

EXAMPLE 36
The preparation of 2,4-dimethyl-3-ethyl-5-carbethoxy-pyrrole



As in Example 32 but using 3-ethyl-4-methyl-5-carbethoxy-pyrrole [6]. It formed colourless prisms (53%), m.p. 91—92°, 89—90° when mixed with authentic material of m.p. 89—90° [7]. Anal. Calc. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.69; H, 8.72; N, 7.19.
6) H. Fischer and H. Orth, loc, cit., p. 241.
7) F. K. Sinaigo and H. Adkins, J. Amer. Chem. Soc., *58*, 709 (1936).

EXAMPLE 37
The preparation of 2,3-diethyl-4-methyl-5-carbethoxy-pyrrole

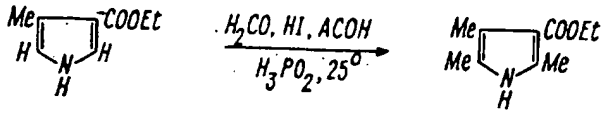


As in Example 32 but using 3-ethyl-4-methyl-5-carbethoxy-pyrrole and paraldehyde. Colourless prisms (64%), m.p. 71—73° (lit. [8] 73—74°). Anal. Calc. for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.67. Found: C, 68.71; H, 9.11; N, 6.84.

8) S. F. MacDonald and A. Markovac, Canad. J. Chem., *43*, 3247 (1965).

EXAMPLE 38

2,4,5-Trimethyl-3-carbethoxy-pyrrole

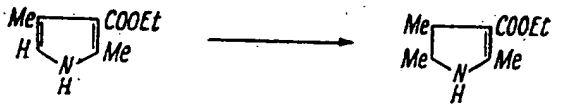


As in Example 32 but using 3-methyl-4-carbethoxy-pyrrole [9]. The product (70%) formed colourless needles, m.p. 103—105° unchanged on admixture with the product of Example 39 below.

9) H. Fischer and H. Orth, loc. cit. p. 246.

EXAMPLE 39

2,4,5-Trimethyl-3-carbethoxy-pyrrole



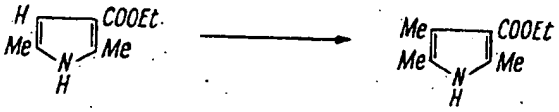
As in Example 32 but using 2,4-dimethyl-3-carbethoxy-pyrrole [10]. It formed colourless needles (67%). m.p. 102—104° (lit [11] 104—105°). Anal. Found: C, 66.12; H, 8.46; N, 7.85.

10) H. Fischer and H. Orth, loc. cit., p. 247.

11) H. Fischer and H. Orth, loc. cit., p. 248.

EXAMPLE 40

2,4,5-Trimethyl-3-carbethoxy-pyrrole



As in Example 32 but using 2,5-dimethyl-3-carbethoxy-pyrrole [12]. Colourless needles (70%), m.p. 103—105°. Anal. Found: C, 66.10; H, 8.30; N, 7.81.

12) H. Fischer and H. Orth, loc. cit., p. 247.

EXAMPLE 41

2,4-Dimethyl-3,5-dicarbethoxy-pyrrole

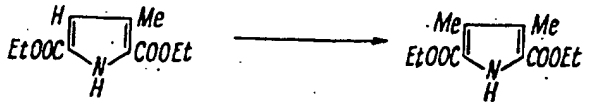
As in Example 32 but using 2-methyl-3,5-dicarbethoxy-pyrrole [13] and stirring for 1/2 hr then pouring the mixture (containing an insoluble labile complex of the product with iodine) into water. Colourless needles (70%), m.p. 135° (lit [14]) 136) from methanol, Anal. Calc. for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.16, H, 7.10; N, 5.80.

13) H. Fischer and H. Orth, loc. cit., p. 255.

14) H. Fischer and H. Orth, loc. cit., p. 255.

EXAMPLE 42

3,4-Dimethyl-2,5-dicarbethoxy-pyrrole

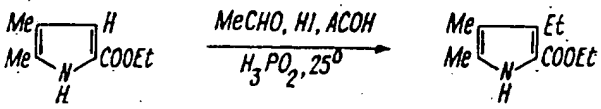


As in Example 32 but using 3-methyl-2,5-dicarbethoxy-pyrrole [15] and stirring at 45° for 3 hrs to redissolve a compound containing iodine which precipitated. It formed colourless crystals (45%) from n-pentane, m.p. 66—68°. Anal Calc. for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 59.93; H, 7.21; N, 6.06.

15) A. H. Corwin and J. L. Straughn, loc. cit.

EXAMPLE 43

2,3-Dimethyl-4-ethyl-5-carbethoxy-pyrrole

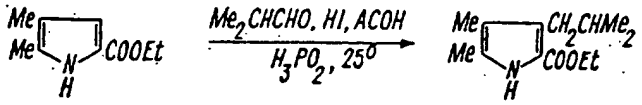


As in Example 32 but using 2,3-dimethyl-5-carbethoxy-pyrrole and paraldehyde. Colourless prisms (51%), m.p. 95—97° (lit [16] m.p. 97°). Anal. Calc. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.59; H, 8.79; N, 7.23.

16) H. Fischer and H. Orth, loc. cit., p. 242.

EXAMPLE 44

2,3-Dimethyl-4-isobutyl-5-carbethoxy-pyrrole



As in example 32 but using 2,3-dimethyl-5-carbethoxy-pyrrole and isobutyraldehyde, pouring the mixture into water after 3 hrs and extracting the product from the alkaline mixture with ether. It was distilled (70°, 1×10^{-4} mm) and crystallized from pentane as colourless prisms (45%), m.p. 109—111°. Anal. Calc. for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 70.23; H, 9.79; N, 6.27.

EXAMPLE 45

2,3-Dimethyl-4-n-heptyl-5-carbethoxy-pyrrole

Obtained as in Example 44 using 2,3-dimethyl-5-carbethoxy-pyrrole and n-heptaldehyde, the product (b.p. 100°, 1×10^{-3} mm) formed colourless crystals (47%) from pentane, m.p. 68—69°. Anal. Calc. for $C_{16}H_{29}NO_2$: C, 72.41, H, 10.26; N, 5.28. Found: C, 72.23; H, 10.27; N, 5.15.

EXAMPLE 46

2,3-Dimethyl-4-n-dodecyl-5-carbethoxy-pyrrole

As in Example 32 but using 2,3-dimethyl-5-carbethoxy-pyrrole and laurylaldehyde and stirring for 3 hrs. It formed colourless prisms (35%), m.p. 70—71°. Anal. Calc. for $C_{21}H_{37}NO_2$: C, 75.17; H, 11.12; N, 4.18. Found: C, 75.08; H, 11.04; N, 4.30.

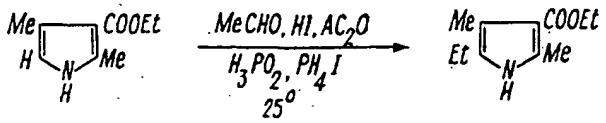
EXAMPLE 47

2,3-Dimethyl-4-n-octadecyl-5-carbethoxy-pyrrole

Obtained as in Example 44 using 2,3-dimethyl-5-carbethoxy-pyrrole and the trimer of stearaldehyde. The product (b.p. 145—150°, 1×10^{-4} mm) formed colour-

less crystals (30%) from ether-n-pentane, m.p. 78—80°. Anal. Calc. for $C_{27}H_{49}NO_2$: C, 77.27; H, 11.77; N, 3.34. Found: C, 77.17; H, 11.68; N, 3.42.

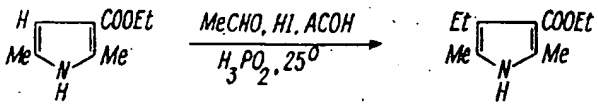
EXAMPLE 48
2,4-Dimethyl-5-ethyl-3-carbethoxy-pyrrole



2,4-Dimethyl-3-carbethoxy-pyrrole (0.668 g) was dissolved in a mixture of hydriodic acid (10 ml), acetic anhydride (10 ml) and hypophosphorous acid (2 ml). Paraldehyde (0.75 ml) was added. The solution was stirred 5 min., decolorized with phosphonium iodide, and poured into ice water. The cooled mixture was brought to pH 8 with ammonium hydroxide. The product was filtered off and distilled (90—100°, 5×10^{-4} mm), giving colourless crystals (53%), m.p. 108—109° after changing to prisms at 105°. For analysis, it was recrystallized from hexane as prismatic rods, m.p. 107—109° (lit [17] 106—107°). Anal. Calc. for $C_{14}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.31; H, 8.72; N, 7.08.

17) L. Knorr and K. Hess, Chem. Ber., *44*, 2762 (1911); *45* 2626, (1912), Note 1.

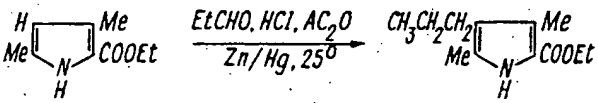
EXAMPLE 49
2,5-Dimethyl-3-ethyl-4-carbethoxy-pyrrole



As in Example 32 but using 2,5-dimethyl-3-carbethoxy-pyrrole and paraldehyde. Colourless crystals (75%), m.p. 105—107° (lit [18] 106—107°). Anal. Calc. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.54; H, 8.69; N, 7.28.

18) E. Vecchi, Gazz. chim. ital., *44*, I, 473 (1914).

EXAMPLE 50
2,4-Dimethyl-3-n-propyl-5-carbethoxy-pyrrole



Acetic anhydride (20 ml) was added to stirred and cooled concentrated hydrochloric acid (5 ml), and 2,4-dimethyl-5-carbethoxy-pyrrole (0.668 g) was dissolved in this. Propionaldehyde (0.6 ml) and amalgamated zinc (10 g, 20 mesh) was added, the mixture stirred 15 min, at 20—25° then decanted into ice water (100 ml). The solid was distilled (80—95°, 1×10^{-4} mm) and crystallized from aqueous ethanol as colourless irregular prisms (48%), m.p. 99—99.5° (lit [19] 98°). Anal. Calc. for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.69. Found: C, 68.75; H, 9.19; N, 6.89.

19) H. Fischer, M. Goldschmidt and W. Nussler, Annalen, *486*, 34 (1931).

EXAMPLE 51
2,4-Dimethyl-3-isopropyl-5-carbethoxy-pyrrole

As Example 50 but using acetone. The colourless crude product (50%), m.p. 105—108° after changing to hexagonal plates, was purified in the same way to give irregular plates, m.p. 105—106.5°. Anal. Calc. for $C_{12}H_{19}NO_2$: C, 68.86, H, 9.15; N, 6.69. Found: C, 68.70; H, 8.98; N, 6.79.

EXAMPLE 52

2,4-Dimethyl-3-n-butyl-5-carbethoxy-pyrrole

As Example 50 but using n-butyraldehyde. The colourless crude product (75%), m.p. 99—103°, was distilled (to 115°, 1×10^{-3} mm) and crystallized from aqueous ethanol as colourless plates, m.p. 101—103°. Anal. Calc. for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.84; H, 9.37; N, 6.37.

EXAMPLE 53

2,4-Dimethyl-3-n-heptyl-5-carbethoxy-pyrrole

As Example 50 but using n-heptaldehyde. After pouring the mixture into water, the product was extracted with ether and distilled (100°, 1×10^{-4} mm) to give colourless crystals, m.p. 47—49°. Anal. Calc. for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.26; N, 5.28. Found: C, 72.60; H, 10.11; N, 5.23.

EXAMPLE 54

2,4-Dimethyl-3-n-dodecyl-5-carbethoxy-pyrrole

As Example 50 but using lauraldehyde, stirring for 1 hr. at 25—30° and pouring the solution into water (100 ml) containing ammonium hydroxide (5 ml) and Girard's reagent "T" (2 g). After two distillations (130°, 1×10^{-4} mm) it formed colourless crystals (27%), m.p. 65—67°. Anal. Calc. for $C_{21}H_{37}NO_2$: C, 75.17; H, 11.12; N, 4.18. Found: C, 74.95; H, 11.01; N, 4.24.

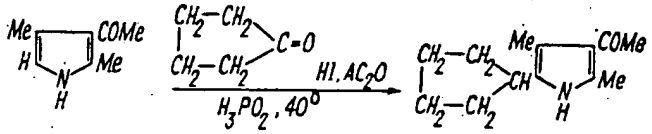
EXAMPLE 55

2,4-Dimethyl-3-n-octadecyl-5-carbethoxy-pyrrole

As Example 50 but using stearaldehyde trimer and stirring for 3 hr. at 25°. The solution was poured into water and the mixture made alkaline with ammonia. The product was extracted with ether, distilled (145—150° 1×10^{-4} mm) and crystallized from ether-pentane as colourless crystals (30%), m.p. 76—78°. Anal. Calc. for $C_{27}H_{49}NO_2$: C, 77.27; H, 11.77; N, 3.34. Found: C, 77.11; H, 11.71; N, 3.27.

EXAMPLE 56

2,4-Dimethyl-3-acetyl-5-cyclopentyl-pyrrole

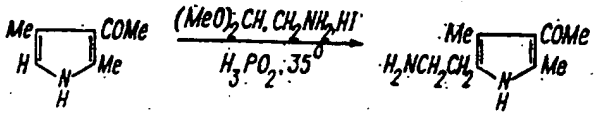


2,4-Dimethyl-3-acetyl-pyrrole (0.548 g) was dissolved in a mixture of hydriodic acid (10 ml), acetic anhydride (10 ml) and hypophosphorous acid (2 ml). The solution was stirred at 40° while cyclopentanone (1.5 ml) was added in three portions over 3/4 hr. After stirring an additional 1/2 hr., the solution was poured into ice water (125 ml) and the pale yellow product (95%), m.p. 161.5—163.5 after changing to prisms at ca 140°, separated. For analysis it was recrystallized successively from hexane, from aqueous methanol and again from n-hexane as pale pink prisms m.p. 167.5—168° (lit [20], 164.5—165.5°). Anal. Calc. for $C_{13}H_{19}NO$: C, 76.05, H, 9.33; N, 6.82. Found: C, 76.12; H, 9.21; N, 6.65.

20) Endo Laboratories Inc. (by K. Schoen and I. J. Pachter). Belg. Pat. 670,796, Jan. 31, 1966; cf. C.A. 65, 16943 (1966).

EXAMPLE 57

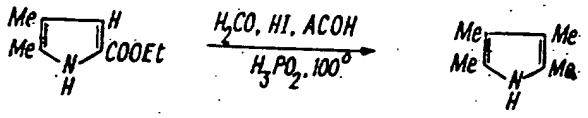
2,4-Dimethyl-3-acetyl-5-(2-amino-ethyl)-pyrrole



Aminoacetaldehyde dimethyl acetal (0.75 ml) was added to a stirred solution of 2,4-dimethyl-3-acetyl-pyrrole (0.548 g) in 10 ml of hydriodic acid and 2 ml of

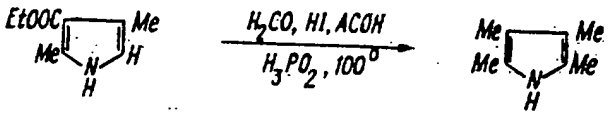
hypophosphorous acid. The solution was stirred for 4 hr. at 35° then evaporated in a shallow dish in a vacuum dessicator, finally at 0.1 mm, and the residue twice slurried and filtered with acetone. The clarified solution of the solid in water (5 ml) was made strongly alkaline with KOH, saturated with potassium carbonate, and extracted repeatedly with ether. The ether solution (125 ml) was concentrated, adding n-pentane toward the end, to precipitate the product (29%) as pale yellow prisms, m.p. 106.5—107.5°. Anal. Calc. for $C_{10}H_{16}N_2O$: C, 66.63; H, 8.95; N, 15.54; neut. equiv. 180. Found: C, 66.51; H, 8.89; N, 15.62; neut. equiv. 182.

EXAMPLE 58
Tetramethyl-pyrrole



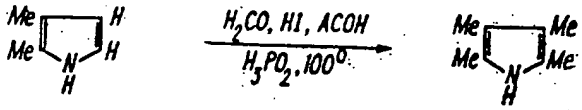
A solution of 2,3-dimethyl-5-carbethoxy-pyrrole (0.82 g) in acetic acid (10 ml), hydriodic acid (10 ml), hypophosphorous acid (2ml) and paraformaldehyde (0.6 g) was stirred and heated at 100° under nitrogen for 3 hr. then poured into water. The mixture was made alkaline with ammonia and extracted with ether. The ether was evaporated and the residue distilled (65°, 15 mm) to give the product (53%) m.p. 105—107°.

EXAMPLE 59
Tetramethyl-pyrrole



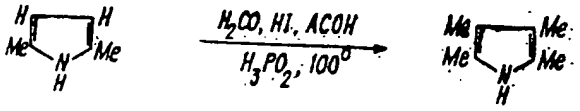
As in Example 58 using 2,4-dimethyl-3-carbethoxy-pyrrole to obtain 0.32 g (53%), m.p. 105—107°. Anal. Calc. for $C_8H_{13}N$: C, 77.99; H, 10.64; N, 11.37. Found: C, 77.96; H, 10.43; N, 11.47.

EXAMPLE 60
Tetramethyl-pyrrole



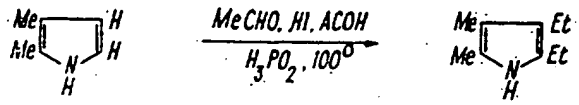
As in Example 58, using 2,3-dimethyl-pyrrole (2 g), acetic acid (50 ml), hydriodic acid (50 ml), hypophosphorous acid (5 ml) and paraformaldehyde (1.2 g). Yield 51%, m.p. 105—107°. Anal. Found: C, 77.81; H, 10.32; N, 11.45.

EXAMPLE 61
Tetramethyl-pyrrole



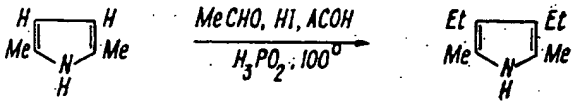
As in Example 60, using 2,5-dimethyl-pyrrole. Yield 49%, m.p. 105—107°.

EXAMPLE 62
2,3-Dimethyl-4,5-diethyl-pyrrole



As in Example 58, using 2,3-dimethyl-pyrrole (1.6 g), acetic acid (40 ml), hydriodic acid (40 ml), hypophosphorous acid (8 ml) and paraldehyde (1.4 ml). The product (48%) was an oil, b.p. 45—47° (0.05 mm). Anal. Calc. for $C_{10}H_{17}N$: C, 79.40; H, 11.34; N, 9.26. Found: C, 79.09; H, 11.27; N, 9.37.

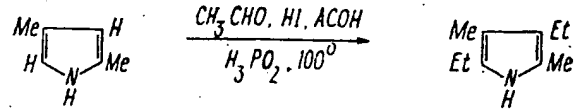
EXAMPLE 63
2,5-Dimethyl-3,4-diethyl-pyrrole [21]



As in Example 58, using 2,5-dimethyl-pyrrole (2 g), acetic acid (50 ml), hydriodic acid (50 ml), hypophosphorous acid (10 ml) and paraldehyde (1.4 ml). The product (46%) was an oil, b.p. 48—50° (0.05 mm). Anal. Calc. for $C_{10}H_{17}N$: C, 79.40; H, 11.34; N, 9.26. Found: C, 79.21; H, 11.53; N, 9.09.

21) cf. H. Fischer and H Orth. loc. cit., p. 58,.

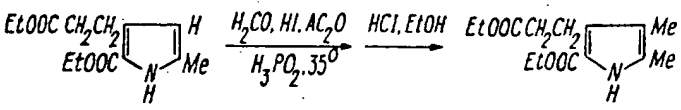
EXAMPLE 64
2,4-Dimethyl-3,5-diethyl-pyrrole [22]



As in Example 62, using 2,4-dimethyl-pyrrole. The product was an oil (56%), b.p. 50—52° (0.06 mm). Anal. Calc. for $C_{10}H_{17}N$: C, 79.40; H, 11.34; N, 9.26. Found: C, 79.22; H, 11.19; N, 9.44.

22) cf. H. Fischer and H. Orth. loc. cit., p. 58; F. K. Sinaigo and H. Adkins, loc. cit.

EXAMPLE 65
2,3-Dimethyl-5-carboxy-pyrrole-4-propionic acid Diethyl Ester



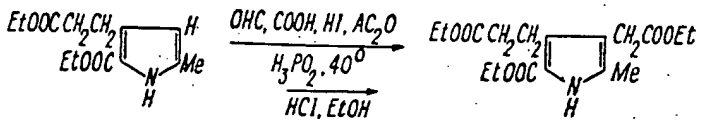
2-Methyl-5-carboxy-pyrrole-4-propionic acid diethyl ester [23] (506 mg) was dissolved in hydriodic acid (5 ml), acetic anhydride (5 ml) and hypophosphorous acid (1 ml). Paraformaldehyde (120 mg) was added, and the mixture was stirred for 25 min. then evaporated (rotary evaporator, 25° then 35° bath, finally 0.5 mm). The residue was rubbed with 2 ml of water then left at 0° overnight. The solid was separated, dried and re-esterified by warming to solution in 6% hydrogen chloride in ethanol (3 ml). The solution, after standing at 20° then at 0°, was scratched. The product which separated was recrystallized from pentane (thimble) as colourless plates (48%), m.p.

90.5—91.5° unchanged when mixed with authentic material [24]. Anal. Calc. for $C_{14}H_{21}O_4N$: C, 62.90, H, 7.92; N, 5.24. Found: C, 63.06; H, 8.03; N, 5.19.

23) S. F. MacDonald, J. Chem. Soc., 4176 (1952).
24) F. Morsingh and S. F. MacDonald, J. Amer. Chem. Soc., *82*, 4377 (1960).

EXAMPLE 66

2-Methyl-5-carboxy-pyrrole-3-acetic acid-4-propionic acid Triethyl Ester

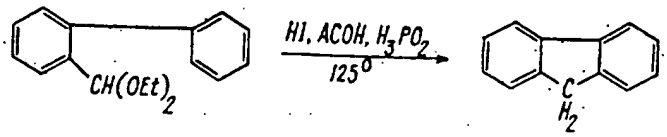


2-Methyl-5-carboxy-pyrrole-4-propionic acid diethyl ester (1.012 g) was dissolved in hydriodic acid (10 ml), acetic anhydride (10 ml) and hypophosphorous acid (2 ml). This solution was stirred at 40° while adding 1.1 g glyoxylic acid monohydrate in 3 portions over 15 min. It was stirred 15 min. more then evaporated (rotary, 25° then 35° bath, finally 0.5 mm). The residue was rubbed with 4 ml of water and left at 0° overnight. The solid was separated, washed with water (2 ml) and dried. It was warmed to solution in 5 ml of 7% hydrogen chloride in ethanol, left 6 hr. at 20° then at 0°. The product which crystallized, together with that from the concentrated and cooled mother liquor, was recrystallized from pentane (thimble) as long colourless needles (1.022 g, 75%), m.p. 66—66.5°, undepressed when mixed with authentic material [25]. Anal. Calc. for $C_{17}H_{23}NO_6$: C, 60.16; H, 7.43; N, 4.13. Found: C, 60.40; H, 7.65; N, 4.31.

25) S. F. MacDonald and R. J. Stedman, Canad. J. Chem., *33*, 458 (1955).

EXAMPLE 67

Fluorene from 2-biphenyl-carboxaldehyde diethyl acetal



Hydriodic acid (10 ml) and hypophosphorous acid (1 ml) were heated and stirred at ca. 100° while 1.024 g of 2-biphenyl-carboxaldehyde diethyl acetal (m.p. 63°, obtained from 2-biphenyl-magnesium iodide and ethyl orthoformate, biphenyl being removed from the crude product by draining in tile then steam-distillation. Anal. Calc. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.48; H, 7.84) in 5 ml of acetic acid was added. The mixture was stirred and slowly distilled until the vapour reached 125° after 1 hr. The combined distillate and residue were diluted with water and the product isolated using ether. It was sublimed at <100° (5×10^{-4} mm) and crystallized from methanol as colourless prisms (83%, m.p. 117.5—118°, mixed m.p. with authentic fluorene of m.p. 118—119°: 117.5—119°). Anal. Calc. for $C_{13}H_{10}$: C, 93.94; H, 6.06. Found: C, 93.67; H, 6.20.

It will be seen from the above example that an intra molecular reaction takes place, both the alkylatable compound and the carbonyl compound being different groups in the same molecule with the result that ring closure is effected.

In the aforesaid Examples:—

The hypophosphorous acid used was 50%. The hydriodic acid was stored at 0° over phosphonium iodide.

The hydriodic acid-acetic anhydride mixture was best made by adding the acetic anhydride slowly to the hydriodic acid, cooled with water and stirred magnetically, then adding the hypophosphorous acid; otherwise, a yellow solid might form.

The phosphonium iodide was prepared as follows: hydriodic acid (D=1.95, 115 ml) and red phosphorous (50 g) were stirred magnetically in a 250 ml flask, surmounted by a 6" air condenser under a reflux condenser and heated by an oil bath. The bath temperature was slowly raised to 80° held at that temperature for 1-1/2

hr., then slowly raised to 105°. The phosphonium iodide was periodically removed from the air condenser and stored at 0° under hydriodic acid (D 1.95). Yield 74 gm; and the reactant 2,4-dimethyl-3-acetyl-pyrrole was prepared as follows, 2,4-dimethyl-3-acetyl-5-carbethoxy-pyrrole (8 g) and 40 ml of 10% aqueous sodium hydroxide were heated for 4 h at 175° in a Teflon lined brass tube. The contents of the tube were ground up and filtered. The solid was washed with water and distilled (125°, 1×10^{-3} mm) to give a colourless product (4.72 g, 90%), m.p. 140—140.5° (lit 137°, H. Fischer and H. Orth. "Chemie des Pyrrols", Leipzig 1934, I, p. 185). Anal. Calc. for $C_8H_{11}N$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.22; H, 8.21; N, 9.99.

The 2,4-dimethyl-3-acetyl-5-ethyl-pyrrole of Example 20 has been prepared by F. K. Sinaigo and H. Adkins, J.A.C.S. *58*, 709 and is given a m.p. of 157—158. The products of Examples 7, 8, 22, 24, 30 and 56 are known compounds disclosed in Belgian Patent No. 670,796 issued January 31, 1966.

The products of Examples 4, 14, 34, 43 to 47, 50 to 55, 65 and 66 are useful for synthetic and analytic work on natural pigments.

WHAT WE CLAIM IS:—

1. A method of introducing a substituted or unsubstituted alkyl or cycloalkyl group onto at least one ring carbon atom of an alkylatable aromatic compound which comprises reacting the aromatic compound with an aldehyde or ketone, or a compound generating an aldehyde or ketone under the reaction conditions, in the presence of a strong inorganic acid condensing agent and a reducing agent, the aromatic compound and aldehyde or ketone, or compound generating the aldehyde or ketone, being stable (as herein defined) under the conditions of the reaction and the aromatic compound having at least one ring carbon atom having replaceable hydrogen or bearing a substituent removable under the reaction conditions to yield a replaceable hydrogen atom whereby to form with the aldehyde or ketone, or compound generating the aldehyde or ketone under the reaction conditions, an intermediate which is reduced to an alkyl or cycloalkyl derivative of the aromatic compound.

2. A method as claimed in claim 1 in which the aromatic compound is a five membered ring compound containing nitrogen in the ring.

3. A method as claimed in claim 1 in which the aromatic compound is a pyrrole derivative.

4. A method as claimed in claim 1 in which the aromatic compound is a pyrrole substituted by at least one methyl group.

5. A method as claimed in claim 1 in which the aromatic compound is a pyrrole substituted by two methyl groups.

6. A method as claimed in claim 5 in which the pyrrole is substituted by a carbethoxy or acetyl groups or both such groups.

7. A method as claimed in claim 1 in which the aromatic compound is 2,4-dimethyl-5-carbethoxy pyrrole, 2,4 - dimethyl - 3,5 - dicarbethoxy pyrrole, 2 - methyl-3 - carbethoxy pyrrole, 2,4 - dimethyl - 3 - acetal pyrrole, 2 - carbethoxy - 3 - methyl-pyrrole, 2 - methyl - 5 - carbethoxy pyrrole, 2,3 - dimethyl - 5 - carbethoxy pyrrole, 2,4 - dimethyl - 3 - bromo - 5 - carbethoxy pyrrole, 3 - ethyl - 4 - methyl - 5 - carbethoxy pyrrole, 3 - methyl - 4 - carbethoxy pyrrole, 2,5 - dimethyl - 3 - carbethoxy pyrrole, 2 - methyl - 3,5 - dicarbethoxy pyrrole, 3 - methyl - 2,5 - dicarbethoxy pyrrole, 2,3 - dimethyl - 5 - carbethoxy pyrrole, 2,3 - dimethyl pyrrole, 2a,5 - dimethyl pyrrole, 2 - methyl - 5 - carboxy pyrrole - 4 - propionic acid diethyl ester or 2,4-dimethyl pyrrole.

8. A method as claimed in claim 1 in which the aromatic compound is benzene or a derivative thereof.

9. A method as claimed in claim 1 in which the aromatic compound is benzene or benzene substituted by at least one hydroxy, methyl or chlorine group.

10. A method as claimed in claim 1 in which the aromatic compound is a xylene, tetrahydronaphthalene, a phenol or a dichlorobenzene.

11. A method as claimed in claim 1 in which the carbonyl compound has the formula R^3COR^4 where R^3 is hydrogen, alkyl or carboxyl and R^4 is hydrogen, alkyl or aryl, or R^3 and R^4 together with the carbon atom to which they are attached form a cycloalkyl group.

12. A method as claimed in claim 11 in which R^3 is hydrogen, methyl, ethyl, isobutyl, tert. butyl, carboxyl, β-carboxyethyl, β-aminoethyl or β-acetyl ethyl, R^4 is hydrogen, methyl, ethyl, phenyl or 3-acetyl-4-methyl-5-ethoxy-2-pyrrole, or R^3 and R^4 together with the carbon atom to which they are attached form the cyclohexyl group.

13. A method as claimed in claim 1 in which the carbonyl compound is formaldehyde, paraldehyde, acetaldehyde, glyoxylic acid, propionaldehyde, n-butyraldehyde, isobutyraldehyde, heptaldehyde, laurylaldehyde, stearaldehyde, amino-acetaldehyde, acetone, diethylketone, methyl-isobutylketone, cyclohexanone, pyruvic acid, levulinic acid, benzaldehyde, acetophenone, chloroacetone, 2,5-hexane-dione or 2-formyl-3-acetyl-4-methyl-5-carbethoxy pyrrole.

14. A method as claimed in claim 1 in which the carbonyl compound is generated *in situ* from paraformaldehyde or paraldehyde.

15. A method as claimed in claim 1 in which the condensing agent is selected from aqueous HI, HI in acetic acid, HI in heptane, HBr in acetic acid, HCl in acetic acid or H_2SO_4 in acetic acid.

16. A method as claimed in claim 1 in which the reducing agent is hydriodic acid, a mixture of hydriodic acid and phosphonium iodide, hydriodic acid and red phosphorous, a mixture of HI and hypophosphorous acid, zinc in acid, stannous bromide or stannous chloride.

17. A method as claimed in claim 1 in which the condensing agent and reducing agent is hydriodic acid.

18. A method as claimed in claim 1 in which the carbonyl compound and the alkylatable aromatic compound are different groups on the same molecule and intramolecular ring closure is effected.

19. A method of ring alkylating an alkylatable aromatic compound substantially as hereinbefore described in any of the Examples.

20. An aromatic compound which has been ring alkylated by the method claimed in any preceding claim.

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